REMARKS

Claims 22-37 are pending. No amendments to the claims are made in this Response. Claims 22-37 are rejected under 35 U.S.C. § 112 as allegedly lacking adequate written description. Claims 22-37 also stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over the cited art. For reasons presented below, it is requested that the rejections be withdrawn and that the claims be allowed to issue.

I. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 22-37 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor was in possession of the claimed invention at the time the application was filed. Specifically, the Examiner argues that the specification as filed does not correlate the potency of a drug with **(A)** the degree of inhibition of phosphotransfer from DevS (or equivalents) to DevR (or equivalents) or **(B)** the degree of inhibition of loss of phosphate-associated radioactivity in a reaction containing DevS (or equivalents) and DevR (or eqivalents) as outlined in the claims.

A. Inhibition of Phosphotransfer from DevS to DevR

The Examiner points to the following two grounds as supporting her contention that the specification does not correlate potency of a drug with the degree of inhibition of phosphotransfer from DevS (or equivalents) to DevR (or equivalents). First, the

Examiner alleges that the specification "indicates that the potency of the drug is inversely proportional to 'the degree of phosphotransfer-based dephosphorylation of DevR and its single domain derivative' thus implying phosphotransfer from phosphorylated DevR, where the recipient is not disclosed." (Page 3 of the instant Office Action). Second, the Examiner argues that "the rate of dephosphorylation of the phosphorylated species of DevS and Rv2027c do not speak to the degree of phosphotransfer to DevR, nor does Figure 9 or any reference to Figure 9 correlate phosphotransfer from DevS or Rv2027c to DevR to determinations of drug potency." (Page 3 of the instant Office Action). For the reasons outlined below, Applicants respectfully submit that the specification indicates drug potency is inversely proportional to more than merely the one example of phosphotransfer identified by the Examiner and that the specification does provide sufficient data to not only correlate the dephosphorylation of DevS and Rv2027c with phosphotransfer to DevR, but also provides sufficient evidence that inhibition of such phosphotransfer correlates with drug potency.

As a preliminary matter, Applicants point out that the specification clearly identifies phosphotransfer from DevS or Rv2027c to DevR as a point where drug intervention is possible. For example, at paragraph [0092] the specification states (emphasis added),

> The DevR-DevS two-component signal transduction system was identified by subtractive hybridization analysis of virulent H37Rv and an avirulent H37Ra strain of M. tuberculosis (Kinger and Tyagi, 1993). The bonafide nature of this two-component system has been validated at the protein level by establishing the phosphorylation potentials of the respective proteins, which forms the basis of all two-component systems. The biochemical function has been validated for Rv2027c-DevR pathway as well. DevR, DevS

> and Rv2027c proteins have been overexpressed in E. coli, purified and refolded in vitro. The refolded proteins have been utilized in in vitro phosphorylation assays, namely; autophosphorylation of the histidine sensor kinases DevS and Rv2027c and phosphotransfer of the phosphoryl moiety from phosphorylated sensor (DevS/Rv2027c) to DevR. Successful biochemical reconstitution of these two-component systems has provided the means for the development of rapid high-throughput assays to screen compound or drug libraries for lead molecules that could interfere with these signal transduction pathways.

Furthermore, the specification points out that inhibition of the activity of the DevR-DevS two-component signaling system as outlined above has dramatic implications for mycobacterial pathogenicity. For example, in paragraph [0020] the application describes experiments performed by the inventors (which are included in PCT/IN02/00022 and incorporated by reference at paragraph [0232] of the instant application) wherein genetic disruption of the DevR gene leads to attenuation of the strain, rapid clearing, and failure to cause latent tuberculosis. Given that the two component systems such as the one currently claimed function via the transfer of phosphate (and such transfer between the two components in the instant system is evidenced by Figures 9 and 10, as discussed in detail below) such genetic DevR disruption is functionally equivalent to the claimed inhibition of phosphotransfer. Accordingly, as the level of inhibition of phosphotransfer increases, the situation increasingly mirrors the genetically disrupted DevR strain and thus drugs that function to inhibit phosphotransfer to a higher extent will be more potent than those that do not.

With regard to the Examiner's second ground for asserting that that the specification does not correlate potency of a drug with the degree of inhibition of

phosphotransfer from DevS (or equivalents) to DevR (or equivalents), Applicants respectfully submit that, contrary to the Examiner's allegation, Figures 9 and 10 do establish that dephosphorylation of DevS or Rc2027c does correlate with phosphotransfer to DevR. In particular, the specification clearly identifies that DevS (or equivalents) will remain phosphorylated for up to four hours unless presented with the opportunity to transfer the phosphate to DevR (or equivalents). In the presence of DevR (or equivalents) the dephosphorylation proceeds within minutes and a concomitant increase in phosphorylation of DevR is observed (See Figure 9). Furthermore, this dephosphorylation and concomitant increase in phosphorylation of DevR is not observed in specific DevR mutants (See Figure 10). In light of the initial stability of phosphorylated DevS and the transfer of phosphate, or lack thereof, depicted in Figures 9 and 10, there is no basis for the examiner's contention that dephosphorylation of DevS fails to correlate with phosphotransfer to DevR.

Applicants also submit that inhibition of phosphotransfer from DevS or Rv2027c to DevR does correlate with drug potency. As pointed out above, inhibition of DevR function leads to attenuation of the strain, rapid clearing, and failure to cause latent tuberculosis. Thus, as the level of inhibition of phosphotransfer from DevS or Rv2027c to DevR increases, the situation will increasingly mirror the genetically disrupted DevR strain and therefore drugs that function to inhibit phosphotransfer from DevS or Rv2027c to DevR to a higher extent can be expected to be more potent than those that do not.

B. Loss of Phosphate-Associated Radioactivity from DevS or DevR

The Examiner uses similar arguments in asserting that the specification does not disclose the determination of the drug potential of the test compound wherein the potency of the drug is inversely proportional to 'the degree of loss of phosphate-associated radioactivity' from DevS (or equivalents) or DevR (or equivalents) in a reaction containing DevS and DevR (or their equivalents). In making this rejection, the Examiner states :

> Though paragraph [178] indicates that in screening of inhibitors, 'presence of a true inhibitor will not lead to reduction of retention of radioactivity on the filter,' the specification does not specify that there is a clear relationship between drug potential and loss of phosphate-associated radioactivity. There is no teaching that any reduction of retention of radioactivity on the filter determines anti-mycobaterial drug potential.

(Page 4 of the instant Office Action)

Accordingly, as above, the Examiner contends that the specification fails to establish a correlation between the observed effect of a potential anti-mycobacterial drug on the retention of radioactivity by DevS (or equivalents) and DevR (or equivalents) when they are present in the same reaction, and therefore measuring the amount of retained radioactivity does not allow for a determination of the potency of the drug. Applicants respectfully disagree with the Examiner's position.

As pointed out in the paragraph cited by the Examiner, a drug capable of interfering with the loss of phosphate-associated radioactivity would be considered a "true inhibitor" of DevS/DevR function. This statement is supported by the data in Figures 14A and 14B, where autophosphorylation of immobilized DevS or Rv2027c is

followed by phosphotransfer subsequent dephosphorylation of DevR. Accordingly, the extent to which any drug would inhibit loss of phosphate-associated radioactivity in such a system would essentially be equivalent to a situation where DevR had been rendered non-functional. Given that non-functional DevR has been established as leading to attenuation of the strain, rapid clearing, and failure to cause latent tuberculosis, the potency of any drug capable of inhibiting the loss of phosphate-associated radioactivity in the instant system would increase as a function of its capability to inhibit.

In light of the foregoing, Applicants respectfully submit that the claims are directed to subject matter that was described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor was in possession of the claimed invention at the time the application was filed. Furthermore, Applicants respectfully submit that specification provides clear support for all of the claim language and thus no new matter has been introduced during the prosecution of this application. Accordingly, withdrawal of the instant rejection is respectfully requested.

II. Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 22-37 under §103(a) as being unpatentable over Hoch et al., US Patent No. 6,043,045, in view of Dasgupta et al., Tubercle and Lung Disease, 80(3):141-159 (2000). The examiner argues that Hoch et al. teach methods of identifying new drugs based on inhibition of phosphorylation of a *B. subtilis* two-component system (SpoOF and KinA), and thus such methods could be combined with the disclosure of the DevS-DevR two component system in Dasgupta et al. to render the instant claims obvious. In particular, the examiner states that it would

have been obvious to a person of ordinary skill in the art to apply the methods of Hoch et al. to the two component system described in Dasgupta et al. because Dasgupta's two component system comprise histidine protein kinases, "thus being appropriate as a target of the Hoch invention."

Applicants respectfully point out that the examiner has not met his burden of establishing a prima facie case of obviousness. The Examiner must establish that one of skill in the art would have a reasonable expectation of success in combining the methods described in Hoch et al. with the teachings of Dasgupta et al. to arrive at the methods encompassed by the pending claims. This has not been done.

Applicants respectfully submit that the Examiner's rejection relies on improper hindsight, using the instant claims as a roadmap to string together the cited references. Specifically, the examiner argues that Dasgupta et al. teach that the DevR/DevS two-component system function by phosphotransfer and thus by using the methods of Hoch et al. it would have been obvious to identify a correlation between drug potency and the rate of phosphotransfer. However, it was not until the filing of the instant application that phosphotransfer from DevS (or equivalents) to DevR (or equivalents) was identified. Importantly, Dasgupta et al. does not provide any support for arguing that inhibition of phosphotransfer correlates with drug potency. In fact, Dasgupta et al. does not even provide any data establishing that either component is even phosphorylated, let alone that they transfer phosphates between themselves. At best Dasgupta et al teaches that the two components contain kinase domains, but fails to disclose if they are functional and if so, the identity of their substrates. Although these references may suggest that making some specified modification should be tried,

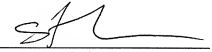
however, "obvious to try" is not the applicable standard here. While KSR v. Teleflex (550 U.S. __, slip opinion at 17 (2007)) suggests that "obvious to try" may be an acceptable basis for finding obviousness in some circumstances, it does not apply in situations such as this one where the outcome cannot be reasonably predicted. (In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)). Given that no knowledge concerning the mechanism of action of the DevS-DevR two component system was available until the filing of this application, there is no basis for finding that the outcome could have been reasonably predicted. In light of the foregoing, Applicants respectfully request withdrawal of the pending rejections under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants respectfully request consideration of the arguments submitted herewith and prompt allowance thereof. Applicants enclose herewith the fee for a three-month extension of time. Should any additional fee be required, or if any overpayment has been made, the Commissioner is hereby authorized to charge any fees, or credit any overpayments made, to Deposit Account 02-4377.

Respectfully submitted,

BAKER BOTTS L.L.P.

By: 

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